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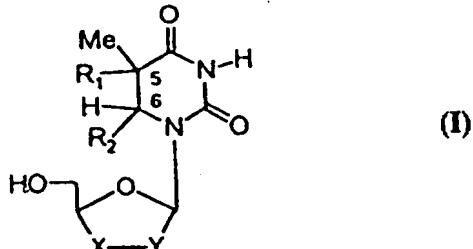
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(54) Title: DIHYDROPYRIMIDINE NUCLEOSIDES WITH ANTVIRAL PROPERTIES

(57) Abstract

Pharmaceutical compounds of general formula (I) have been prepared and non-toxic pharmaceutically acceptable salts thereof, wherein R₁ is a halogen substituent; R₂ is a member selected from the group consisting of alkoxy, hydroxy and azido; and X-Y is a member selected from the group consisting of CH(N₃)-CH₂,

CH(F)-CH₂ and CH=CH. Halogen denotes an iodo, bromo, chloro and fluoro atom. Alkoxy denotes a straight or branched chain moiety having 1-16 carbon atoms. Compounds of formula (I) can exist as the (5R, 6R), (5S, 6S), (5R, 6S) and (5S, 6R) diastereomers which differ in configuration at positions C-5 and C-6. These compounds exhibit anti-human immunodeficiency virus activity (anti-HIV) and are useful in the treatment of acquired immunodeficiency syndrome (AIDS) and AIDS-related complex.



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DIHYDROPYRIMIDINE NUCLEOSIDES WITH ANTIVIRAL PROPERTIES

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FIELD OF THE INVENTION

The present invention relates to pharmaceutical compounds. More particularly, the invention provides new 10 unnatural 5,6-dihydropyrimidine nucleoside derivatives, or non-toxic pharmaceutically acceptable salts thereof, having useful physiological antiviral effects, particularly anti-human immunodeficiency virus (anti-HIV) properties which are useful in the treatment of acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. The 15 invention relates to such compounds and compositions thereof, and to processes for making and using them.

BACKGROUND OF THE INVENTION

20

Human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT) plays an important role in the life cycle of the virus and has been a major target for the design of drugs to combat AIDS. One class of HIV-1 RT 25 inhibitors are pyrimidine nucleoside analogs such as 3'-azido-3'-deoxythymidine (AZT), 3'-fluoro-3'-deoxythymidine (FT) and 2',3'-didehydro-2',3'-dideoxythymidine (d4T). These compounds are converted into their triphosphates by cellular enzymes, the triphosphates 30 are then recognized by HIV-1 RT as substrates. The corresponding nucleoside monophosphate moiety is incorporated into deoxyribonucleic acid (DNA) chains. Since these analogs lack a 3'-hydroxyl group, this incorporation leads to DNA chain termination. Although AZT appears to be 35 temporarily effective in decreasing mortality and morbidity in some patients with AIDS, or AIDS-related complex, bone marrow toxicity and anemia are very severe [see the Medical

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Letter, 28 , 107 (1986)]. Frequently administered high doses of AZT must be used to maintain a therapeutic drug level due to its short biological half-life of one hour [see D.D. Richman, M.A. Fischl, M.H. Grieco, M.S. Gottlieb, P.A. Volberding, O.L. Laskin, J.M. Leedom, J. Groopman, D. Mildvan, M.S. Hirsch, G.G. Jackson, D.T. Durack and S. Nusinoff-Lehrman, N. Engl. J. Med., 317, 10 192 (1987)] which is attributed to its rapid metabolism to the inactive 5'-O-glucuronide (GAZT) and the highly toxic 3'- amino-3'-deoxythymidine (AMT) [see E.M. Cretton, M.-Y. Xie, R.J. Bevan, N.M. Goudgoan, R.F. Schinazi and J.-P. Sommadossi, Mol. Pharmacol., 39 , 258 (1991)]. Since AZT 15 does not penetrate into brain tissue from the cerebral spinal fluid, it does not effectively suppress viral replication in the brain and it is believed that the HIV replicates more rapidly in the central nervous system (CNS), the CNS serving as a reservoir for the virus in the body.

A correlation between lipophilicity, membrane permeability and CNS penetration has long been established [see C. Hansch, A.R. Stewart, S.M. Anderson and D. Bentley, J. Med. Chem., 11 , 1 (1968); D.P. Hall and C.G. Zubrod, 25 Ann. Rev. Pharmacol., 2 , 109 (1962); W.H. Oldendorf, Proc. Soc. Exp. Biol. Med., 147 , 813 (1974)]. The lipophilicity of a compound can be described as the partition coefficient (P) of a drug between 1-octanol (lipid phase) and aqueous buffer at a pH of 7. It has been 30 reported that the partition coefficients for AZT, FT and d4T are 0.964, 0.529 and 0.154, respectively [see E.J. Lien, H. Gao and H. Prabhaker, J. Pharm. Sci., 80 , 517 (1991)]. Although AZT is the most lipophilic, it is neither lipophilic nor hydrophilic since it partitions 35 almost equally ($P = 0.964$). Several studies to design more lipophilic compounds, and hence their ability to penetrate into the CNS across the blood-brain-barrier (BBB) have not

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resulted so far in compounds with an acceptable therapeutic potency.

5 Although a number of 5,6-dihydrothymidine analogs of the physiological nucleoside thymidine are known (see A.G. Samuel, H.B. Mereyala and K.N. Ganesh, Nucleosides & Nucleotides, 11 , 49 (1992); R. Teoule, B. Fouque and J. Cadet, Nucl. Acid Res., 2 , 487 (1975); G. Bernardinelli, 10 R. Benhamza and J.M. Tronchet, Acta Cryst. C45 , 1917 (1989)) these analogs act as competitive inhibitors of thymidine kinase at low concentrations (see B. Fouque and R. Teoule, Chemotherapy, 20 , 221 (1974)). Since these analogs do not inhibit reverse transcriptase, they are ineffective in the treatment of AIDS or AIDS-related complex.

It has now been discovered that the introduction of a halogen atom in position 5 in conjunction with an alkoxy, hydroxy or azido substituent in position 6 increase 20 lipophilicity thereby resulting in an increased ability to penetrate into the CNS. Such compounds exhibit anti-human immunodeficiency virus (anti-HIV) activity and may also be useful to treat other clinical conditions such as hepatitis B viral infections and other viral infections.

25 In addition such compounds have a longer biological half-life allowing for a longer duration of action and they exhibit an increasing drug stability and a decreasing toxicity. Alternatively, such compounds may serve as pro-drugs, since a reducing agent (such as 30 glutathione in vivo) would regenerate the 5,6-olefinic bond releasing AZT, FT or d4T.

DETAILED DESCRIPTION OF THE INVENTION

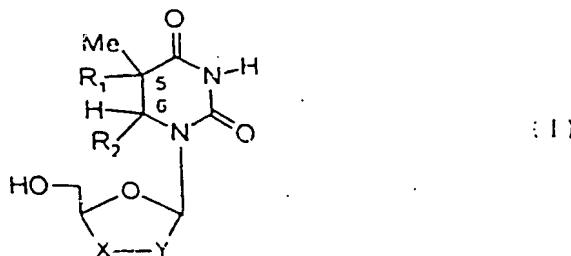
35 The present invention relates to new 5,6-dihydro-pyrimidine derivatives and non-toxic, pharmaceutically acceptable salts thereof (as well as pharmaceutical

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compositions containing them).

The new compounds according to the present
5 invention have the general formula:

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wherein:
R₁ is a halogen; R₂ is a hydroxy, alkoxy group or azido; and
20 X-Y is a member selected from the group CH=CH,
CH(N₃)-CH₂ or CH(F)-CH₂ as well as the non-toxic,
pharmaceutically acceptable salts thereof.

The term "halogen" as used herein means fluorine, chlorine, bromine or iodine.

25 The term "alkoxy" as used herein means substituents of straight and branched chain aliphatic alcohols having from 1 to 16 carbon atoms.

Compounds of formula (I) can exist as one of four possible diastereomers wherein R₁ and R₂ have the meanings given above since an asymmetric carbon is respectively 30 present at the C-5 and C-6 positions.

The term "diastereomer" means the (5R,6R), (5S,6S), (5R,6S) or (5S,6R) configuration.

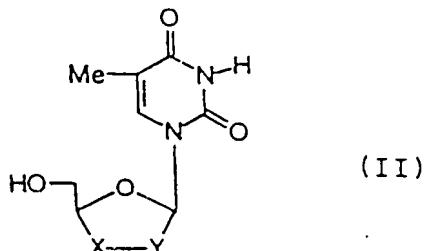
The 5-halo-6-alkoxy-5,6-dihydrothymidine

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derivatives are prepared by reacting a thymidine analog of the formula:

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wherein X-Y is a member selected from the group consisting of $\text{CH}(\text{N}_3)-\text{CH}_2$, $\text{CH}(\text{F})-\text{CH}_2$ and $\text{CH}=\text{CH}$ with an electrophilic source of halogen of the formula:

15



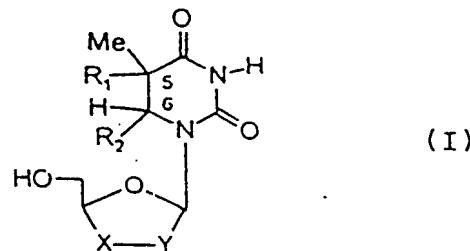
wherein R_1 is an iodo, bromo, chloro or fluoro atom and Z is a member independently selected from the group consisting of iodo, bromo and chloro, in the presence of an alkyl alcohol of the formula:



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wherein R_2 is an alkoxy group wherein the alkyl moiety is a straight or branched aliphatic alkyl chain having from 1 to 16 carbon atoms, allowing the reaction to occur in the temperature range of -78°C to 25°C , preferably in the 0°C to 25°C range, to convert to 5-halo-6-alkoxy-5,6-dihydrothymidine diastereomers of the formula:

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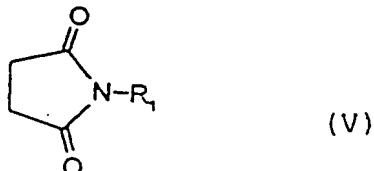
wherein R_1 , R_2 and X-Y are as defined above. The reactions are allowed to take place in inert organic

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solvents such as tetrahydrofuran, dioxane or dimethoxyethane when the alkyl alcohol of formula (IV) is a solid.

5 Alternatively, compounds of formula (I) can also
be prepared by reacting a thymidine analog of formula (II)
wherein X-Y is as defined above, with an electrophilic
source of halogen of the formula:

10



15 wherein R₁ is a member selected from the group consisting
 of iodo, bromo and chloro, in the presence of an alkyl
 alcohol of formula (IV) wherein R₂ is as defined as above
 and glacial acetic acid, allowing the reaction to occur at
 25°C etc. convert to 5-halo-6-alkoxy-5,6-dihydrothymidine
 20 derivatives of the formula (I) wherein R₁, R₂ and X-Y
 are as defined as above. These reactions are allowed to
 take place in inert organic solvents such as dimethoxy-
 ethane, dioxane or tetrahydrofuran (preferably dimethoxy-
 ethane).

25 The 5-halo-6-azido-5,6-dihydrothymidine derivatives are prepared by reacting a thymidine analog of the formula (II) wherein X-Y is as defined as above, with an electrophilic source of halogen of the formula (V) wherein R₁ is as defined above, in an inert organic 30 solvent such as dimethoxyethane, dioxane or tetrahydrofuran, preferably dimethoxyethane, and an alkali metal azide of the formula (VI):

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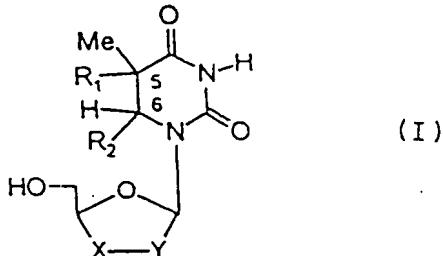


wherein R₂ is an azido group and M is selected from a group consisting of sodium, lithium and potassium, prefer-

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ably sodium, in a water solvent, allowing the reaction to occur in the -5°C to 25°C range to convert to 5-halo-6-5 azido-5,6- dihydrothymidine diastereomers of the formula:

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wherein R₁ is a member selected from the group consisting of iodo, bromo and chloro, R₂ is an azido substituent and X-Y is as defined above.

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The 5-halo-6-hydroxy-5,6-dihydrothymidine derivatives are prepared by reacting a thymidine analog of formula (II) wherein X-Y is as defined above, with an electrophilic source of halogen of the formula (V) wherein R₁ is as defined above, in water as a solvent, allowing the reaction to occur at 0°C to convert to 5-halo-6-hydroxy-5,6-dihydrothymidine diastereomers of the formula (I), wherein R₁ is a member selected from the group consisting of iodo, bromo and chloro, R₂ is a hydroxyl substituent and X-Y is as defined above.

20

More particularly, the compounds listed in the Examples and in Table I, II, and III have been prepared, and through testing, have been found to have anti-human immunodeficiency virus properties (Table IV).

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Suitable pharmaceutically acceptable phosphate forms of these compounds include the 5'-0-monophosphate, 5'-0-diphosphate and 5'-0-triphosphate derivatives.

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These compounds can be administered either parentally, as by injection, or orally. As a liquid carrier, a carrier such as water or polyethylene glycol, or other physiologically acceptable solvents or dispersing liquids can be used. For oral administration, either solid or liquid carriers may be used. One commonly used solid

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carrier is gum acacia, but others are also suitable. An operative dosage range is between about 0.01 and 200 mg/kg, 5 preferably between 0.1 and 20 mg/kg.

The following non-limitative examples illustrate some selective methods for producing the compounds according to the present invention, as well as comparative data illustrating the anti-human immunodeficiency virus 10 (anti-HIV) effect of representative compounds according to the present invention.

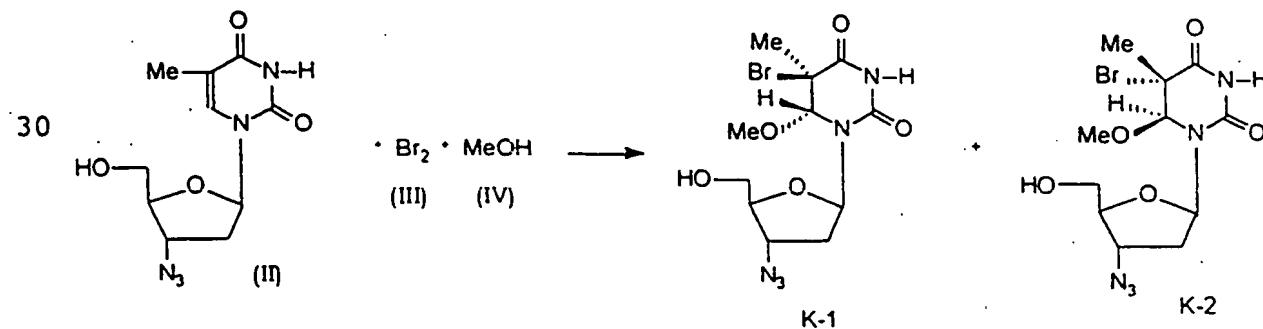
The starting materials for the preparation of compounds of formula (I), viz the thymidine analogs of formula (II), the electrophilic forms of halogen of formula 15 (III) and formula (V), the alkyl alcohols of formula (IV), and azides of formula (VI) are either known or are conveniently prepared from known starting materials from methods known per se.

The following examples are given for the purpose 20 of illustrating the present invention:

Example 1

Preparation of 5-bromo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine:

Schematic for Example 1



35 A freshly prepared solution of methyl hypobromite (bromine in methanol) was added dropwise to a solution of 3'-azido-3'-deoxythymidine (0.2 g, 0.75 mmol) in methanol

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(10 mL) at 25°C with stirring until the light yellow color of the reaction mixture persisted. The reaction was allowed to proceed at 25°C for 20 min prior to neutralization to pH 6 using a solution of methanolic sodium hydroxide. Removal of the solvent in vacuo, dissolution of the residue in methanol (5 mL), adsorption onto silica gel (1 g), removal of the solvent in vacuo, and application of this material to the top of a silica gel column (Merck 7734, 100-200 µM particle size) followed by elution with chloroform-methanol (95:5, v/v) afforded a mixture of the diastereomers K-1 and K-2 (0.225 g, 79%) as a viscous oil. Analysis found: C, 34.40; H, 4.27; N, 17.85. $C_{11}H_{16}BrN_5O_5$. 1/2 H_2O requires: C, 34.12, H, 4.42; N, 18.08. The two diastereomers (5R,6R)-5- bromo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-1) and (5S,6S)-5-bromo-6-methoxy-5,6-dihydro-3'-azido-3'- deoxythymidine (K-2) were separated using Whatman RLK5F silica gel plates (1 mm thickness) using chloroform-methanol (95:5, v/v) as development solvent.

Diastereomer K-1: $[\alpha]_D^{25} = +71.7^\circ$ (c 0.0030, MeOH); R_f 0.61; oil; yield (60 mg, 21%); 1H NMR ($CDCl_3$) δ 1.96 (s, 3H, CH_3), 2.32 and 2.68 (two m, 1H each, H-2'), 3.46 (s, 3H, OCH_3), 3.80 (m, 1H, H-5'), 3.94 (m, 2H, H-4', H-5"), 4.34 (m, 1H, H-3'), 4.95 (s, 1H, H-6), 5.90 (d, $J_{1',2'}=6.0$ Hz, 1H, H-1'), 8.64 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 22.82 (CH_3), 37.04 (C-2'), 53.21 (C-5), 57.41 (OCH_3), 60.06 (C-3'), 62.12 (C-5'), 84.02 (C-4'), 86.66 (C-1'), 89.16 (C-6), 150.58 (C-2 C=O), 167.10 (C-4 C=O).

Diastereomer K-2: $[\alpha]_D^{25} = -43.3^\circ$ (c 0.0021, MeOH); R_f 0.63; oil; yield (0.148 g, 52%); 1H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 2.26 and 2.96 (m, 2H, H-2'), 3.60 (s, 3H, OCH_3), 2.76 (m, 1H, H-5'), 2.94 (m, 1H, H-5"), 4.02 (m, 1H, H-4'), 4.52 (m, 1H, H-3'), 4.59 (s, 1H, H-6), 5.27 (d, $J_{1',2'}=6.0$ Hz, 1H, H-1'), 8.53

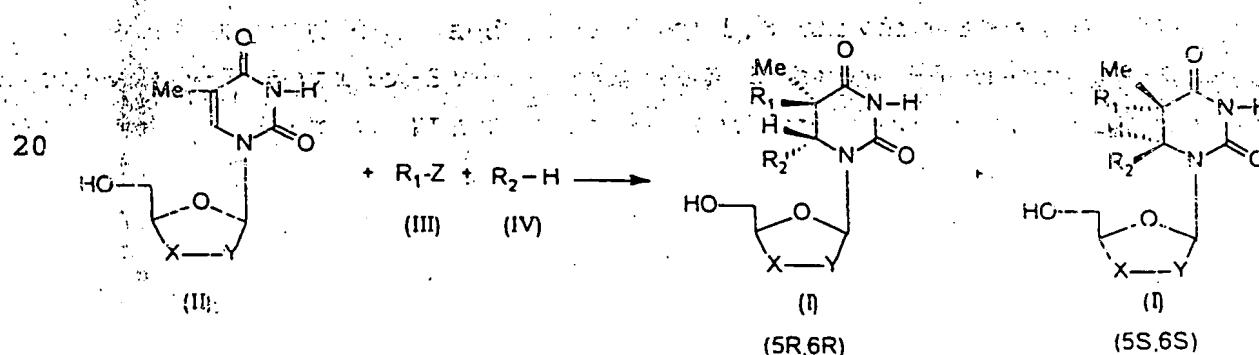
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(s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR (CDCl_3) δ 22.66 (CH_3), 35.01 (C-2'), 53.34 (C-5), 57.15
 5 (OCH₃), 61.48 (C-3') 62.86 (C-5'), 85.05 (C-4'), 92.56 (C-1'), 95.27 (C-6), 150.51 (C-2 C=O), 166.83 (C-4 C=O).

Example 2

10 Utilizing the general procedure of Example 1 and starting from the appropriately substituted compounds of the formula (II), of formula (III) and of formula (IV), as represented in the schematic for Example 2, the following compounds of the formula (I) are prepared:

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Schematic for Example 2Schematic for Example 2

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TABLE (1)
5-halo-6-alkoxy-5,6-dihydrothymidine diastereomers prepared according to Example 2

| Chemical Name | (SR GR) | (SS GS) | (SS GR) | No. | R ₁ | R ₂ | X-Y | R _f a | [α] _D ^b 2S(c, MeOH) | mp. °C |
|---|---------|---------|--------------------------------------|-----|---|----------------|-----------------|------------------|---|--------|
| (5R, 6R)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine | K-3 | Br | OEt | | CH(N ₃) ₂ -CH ₂ | 0.68 | +76.6° (0.0016) | 123-125 | | |
| (5S, 6S)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine | K-4 | Br | OEt | | CH(N ₃) ₂ -CH ₂ | 0.75 | -37.3° (0.0035) | oil | | |
| (5R, 6R)-5-bromo-6-isopropoxy-5,6-dihydro-3'-azido-3'-deoxythymidine | K-5 | Br | O-i-Pr | | CH(N ₃) ₂ -CH ₂ | 0.69 | +72.6° (0.0034) | oil | | |
| (5R, 6R)-5-chloro-6-isopropoxy-5,6-dihydro-3'-azido-3'-deoxythymidine | K-6 | Cl | O-i-Pr | | CH(N ₃) ₂ -CH ₂ | 0.69 | +70.3° (0.0120) | oil | | |
| (5R, 6R)-5-bromo-6-(1-octyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine | K-7 | Br | O(CH ₂) ₇ Me | | CH(N ₃) ₂ -CH ₂ | 0.81 | +41.6° (0.0055) | oil | | |
| (5R, 6R)-5-chloro-6-(1-octyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine | K-8 | Cl | O(CH ₂) ₇ Me | | CH(N ₃) ₂ -CH ₂ | 0.84 | +37.7° (0.0048) | oil | | |
| (5R, 6R)-5-bromo-6-(1-hexadecyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine | K-9 | Br | O(CH ₂) ₁₅ Me | | CH(N ₃) ₂ -CH ₂ | 0.84 | +27.6° (0.0085) | oil | | |
| (5R, 6R)-5-bromo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-10 | Br | OMe | | Cl(F)-CH ₂ | 0.58 | +67.2° (0.0023) | oil | | |
| (5S, 6S)-5-bromo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-11 | Br | OMe | | Cl(F)-CH ₂ | 0.70 | -72.5° (0.0016) | oil | | |
| (5R, 6R)-5-bromo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine | K-12 | Br | OMe | | CH=CH | 0.57b | +66.0° (0.0060) | 93-95 | | |
| (5S, 6S)-5-bromo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine | K-13 | Br | OEt | | CH=CH | 0.57b | -80.0° (0.0036) | oil | | |
| (5R, 6R)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine | K-14 | Br | OEt | | CH=CH | 0.61c | ND ^d | oil | | |
| (5S, 6S)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine | K-15 | Br | OEt | | CH=CH | 0.61c | ND | oil | | |

aCHCl₃MeOH (9:1, v/v) Whatman 25 mM silica gel thin layer plates

bSeparated by HPLC using a Whatman Partisil NG 10/25 ODS C-18 reverse phase column using water-methanol as eluent at a flow rate of 2ml/min

cNot separated by preparative HPLC

dND-not determined

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Example 3

5 Preparation of 5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine.

Chlorine gas (4.7 g) was bubbled slowly into a suspension of 3'-azido-3'-deoxythymidine (10 g, 37.4 mmol) in 98% ethanol (500 mL) at 0°C with stirring until the 10 light yellow-green color of the resulting solution persisted. The pH of this solution was adjusted to 6.5 using a solution of sodium hydroxide in ethanol and the mixture was filtered. Removal of the solvent from the filtrate in vacuo and separation of the residue obtained by elution 15 from a silica gel column using chloroform-methanol (97:3, v/v) as eluent gave (5S,6S)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-17), (5R,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-16), and (5S,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxy- 20 thymidine (K-18), respectively. Analysis found: C, 41.62; H, 5.20; N, 19.81. $C_{12}H_{18}ClN_5O_5$ requires: C, 41.44; H, 5.21; N, 20.14.

Diastereomer K-16: $[\alpha]_D^{25} = +63.0^\circ$ (c 0.019, MeOH); R_f 0.67; mp 118-120°C; yield (8 g, 61.5%); 1H NMR ($CDCl_3$) δ 1.16 (t, J=7 Hz, 3H, OCH_2CH_3), 1.82 (s, 3H, C-5 CH₃), 2.30 (m, 1H, H-2'), 2.64 (m, 2H, H-2' and 5'-OH which exchanges with deuterium oxide), 3.50-3.98 (m, 5H, H-4', H-5', OCH_2CH_3), 4.32 (m, 1H, H-3'), 4.92 (s, 1H, H-6), 5.84 (d, $J_{1',2'}=6.0$ Hz, 1H, H-1'), 8.30 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 14.93 (OCH_2CH_3), 21.76 (C-5 CH₃), 37.04 (C-2'), 60.10 (C-3'), 60.94 (C-5), 62.20 (C-5'), 65.55 (OCH_2CH_3), 84.01 (C-4'), 87.04 (C-1'), 87.92 (C-6), 150.62 (C-2 C=O), 166.62 (C-4 C=O).

35 Diastereomer K-17: $[\alpha]_D^{25} = -15.3^\circ$ (c 0.028, MeOH); R_f 0.72; oil; yield (0.5 g, 3.7%); 1H NMR

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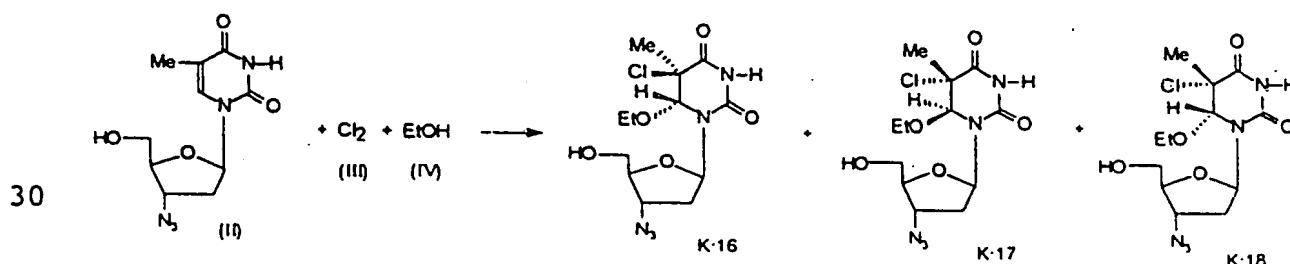
(CDCl₃) δ 1.10 (t, J=7 Hz, 3H, OCH₂CH₃), 1.68 (s, 3H, C-5 CH₃), 2.10 (m, 1H, H-2'), 2.78 (m, 1H, H-2"), 5 3.40-3.92 (m, 5H, H-4', H-5', OCH₂CH₃), 4.36 (m, 1H, H-3'), 4.48 (s, 1H, H-6), 5.16 (d, J_{1'},_{2'}=6.0 Hz, 1H, H-1'), 9.04 (s, 1H, NH, exchanges with deuterium oxide); ¹³C NMR (CDCl₃) δ 14.72 (OCH₂CH₃), 21.58 (C-5 CH₃), 34.94 (C-2'), 61.09 (C-5), 61.56 (C-3'), 62.96 10 (C-5'), 65.50 (OCH₂CH₃), 85.11 (C-4'), 92.78 (C-1'), 93.86 (C-6), 150.49 (C-2 C=O), 166.25 (C-4 C=O).

Diastereomer K-18: [α]_D²⁵ = +42.1° (c 0.009, MeOH); R_f 0.61; oil; yield (3.5 g, 26.7%); ¹H NMR (CDCl₃) δ 1.18 (t, J=7 Hz, 3H, OCH₂CH₃), 1.78 (s, 3H, C-5 CH₃), 2.28 (m, 1H, H-2'), 2.68 (m, 1H, H-2"), 3.20 (br s, 1H, 5'-OH, exchanges with deuterium oxide), 3.60-3.98 (m, 5H, H-4', H-5', OCH₂CH₃), 4.36 (m, 1H, H-3'), 4.82 (s, 1H, H-6), 5.64 (d, J_{1'},_{2'}=6.0 Hz, 1H, H-1'), 8.80 (br s, 1H, NH, exchanges with deuterium oxide); ¹³C NMR (CDCl₃) δ 14.84 (OCH₂CH₃), 25.88 (C-5 CH₃), 36.98 (C-2'), 60.34 (C-3') 62.16 (C-5'), 66.67 (OCH₂CH₃), 66.98 (C-5), 84.15 (C-4'), 87.88 (C-1'), 89.79 (C-6), 151.10 (C-2 C=O), 167.79 (C-4 C=O).

Schematic for Example 3

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Schematic for Example 3



Example 4

Preparation of 5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine.

N-Chlorosuccinimide (0.2 g, 1.5 mmol) was added to a solution of 3'-azido-3'-deoxythymidine (0.2 g, 0.75

-14-

mmol) in methanol (10 mL) and glacial acetic acid (0.6 mL) with stirring and the reaction was allowed to proceed at 5 25°C for 15 h. At this time additional N-chlorosuccinimide (0.2 g, 1.5 mmol) and glacial acetic acid (0.6 mL) were added and the reaction was allowed to proceed at 25°C for 24 h with stirring prior to neutralization to pH 6.5 using methanolic sodium hydroxide. Removal of the solvent in 10 vacuo gave a residue which was dissolved in chloroform (5 mL), the chloroform solution was washed with cold water (2 x 5 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The residue obtained was purified by elution from a 15 silica gel column using chloroform-methanol (95:5, v/v) as eluent to yield a mixture of diastereomers (5R,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-19), and (5S,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-20). Analysis found: C, 39.46; H, 4.87. $\text{C}_{11}\text{H}_{16}\text{ClN}_5\text{O}_5$ requires: C, 39.58; H, 4.83. The two diastereomers K-19 and K-20 were separated 20 by PTLC using Whatman PLK5F silica gel plates (1 mM thickness) using chloroform-methanol (95:5, v/v) as development solvent.

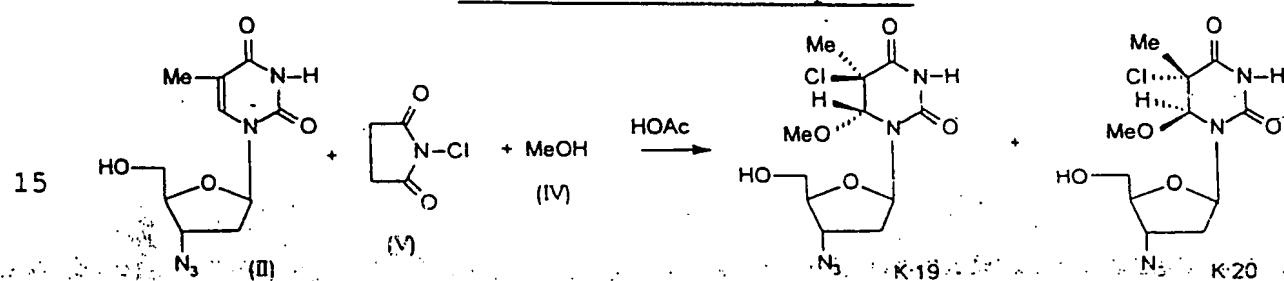
Diastereomer K-19: $[\alpha]_D^{25} = +74.7^\circ$ (c 25 0.0038, MeOH); R_f 0.57; oil; yield (0.1 g, 40%); ^1H NMR (CDCl_3) δ 1.80 (s, 3H, C-5 CH_3), 2.30 and 2.63 (two m, 1H each, H-2'), 3.46 (s, 3H, OCH_3), 3.82 (m, 1H, H-5'), 3.96 (m, 2H, H-4', H-5"), 4.32 (m, 1H, H-3'), 4.90 (s, 1H, H-6), 5.92 (d, $J_{1',2'}=6.0$ Hz, 1H, H-1'), 8.80 (s, 30 1H, NH, exchanges with deuterium oxide); ^{13}C NMR (CDCl_3) δ 21.60 (CH_3), 36.95 (C-2'), 57.36 (OCH_3), 60.04 (C-3'), 60.88 (C-5), 62.05 (C-5'), 83.95 (C-4'), 86.39 (C-1'), 88.62 (C-6), 150.66 (C-2 C=O), 166.71 (C-4 C=O).

35 Diastereomer K-20: $[\alpha]_D^{25} = +39.3^\circ$ (c 0.0059, MeOH), R_f 0.54; oil; yield (45 mg, 18%); ^1H NMR (CDCl_3) δ 1.83 (s, 3H, C-5 CH_3), 2.32 and 2.75 (two m,

-15-

1H each, H-2'), 3.56 (s, 3H, OCH₃), 3.80 (m, 1H, H-5'), 3.98 (m, 2H, H-4', H-5"), 4.40 (m, 1H, H-3'), 4.76 (s, 1H, H-6), 5.78 (d, J_{1',2'}=6.0 Hz, 1H, H-1'), 8.28 (br s, 1H, NH, exchanges with deuterium oxide); ¹³C NMR (CDCl₃) δ 26.05 (CH₃), 37.0 (C-2'), 58.23 (OCH₃), 60.35 (C-3'), 62.34 (C-5'), 66.88 (C-5), 84.25 (C-4'), 88.18 (C-1'), 91.46 (C-6), 150.57 (C-2 C=O), 167.02 (C-4 C=O).

Schematic for Example 4



Example 5

Preparation of 5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine.

N-Bromosuccinimide (80 mg, 0.44 mmol) was added in aliquots to a suspension of 2',3'-didehydro-2',3'-dideoxythymidine (0.1 g, 0.44 mmol) in water (5 mL) at 0°C with stirring. The initial yellow color produced upon addition of each aliquot of N-bromosuccinimide disappeared rapidly. After all the N-bromosuccinimide had been added, the reaction mixture was stirred for 20 min at 0°C. Removal of the solvent in vacuo, dissolution of the residue obtained in ethyl acetate (5 mL), adsorption onto silica gel (1 g), removal of the solvent in vacuo and application of this material to the top of a silica gel column followed by elution with chloroform-methanol (96:4, v/v) as eluent afforded (5R,6R)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine (K-32) and (5S,6S)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine (K-33), respectively. Analysis found: C,

-16-

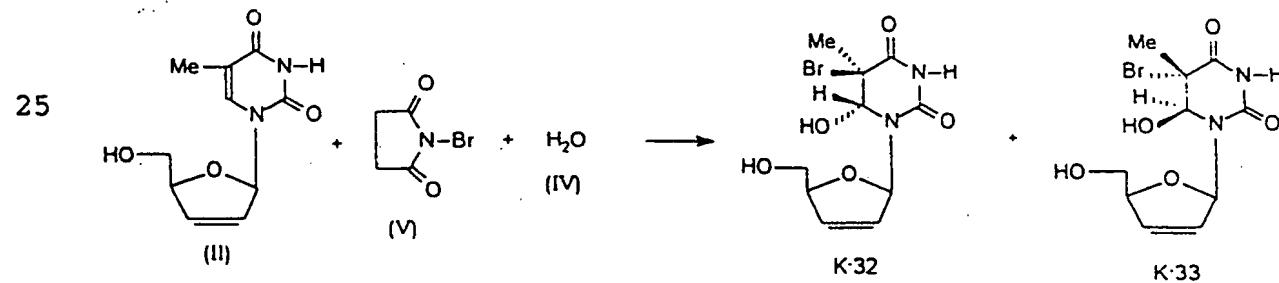
37.89; H, 4.15; N, 8.63. C₁₀H₁₃BrN₂O₅
requires: C, 37.40; H, 4.07; N, 8.72.

5 Diastereomer K-32: [α]_D²⁵ = +31.9° (c.
0.0026, MeOH); R_f 0.42; mp 94–95°C; yield (60 mg, 43%);
¹H NMR (CD₃OD) δ 1.88 (s, 3H, CH₃), 3.74 (m, 2H,
H-5'), 4.80 (m, 1H, H-4'), 5.15 (s, 1H, H-6), 5.90 (m, 1H,
H-3'), 6.30 (m, 1H, H-2'), 6.82 (m, 1H, H-1'); ¹³C NMR
10 (CD₃OD) δ 23.38 (CH₃), 55.29 (C-5), 62.56 (C-5'), 81.76
(C-6), 87.38 (C-4'), 91.77 (C-1'), 127.14 (C-2'), 135.35
(C-3').

15 Diastereomer K-33: [α]_D²⁵ = -32.7° (c.
0.0011, MeOH), R_f 0.35; oil; yield (47 mg, 33.1%); ¹H
NMR (CD₃OD) δ 1.82 (s, 3H, CH₃), 3.74 (m, 2H, H-5'),
4.75 (m, 1H, H-4'), 5.28 (s, 1H, H-6), 5.95 (m, 1H, H-3'),
6.24 (m, 1H, H-2'), 6.78 (m, 1H, H-1'); ¹³C NMR
(CD₃OD) δ 23.30 (CH₃), 54.68 (C-5), 65.07 (C-5'), 80.12
(C-6), 87.71 (C-4'), 90.79 (C-1'), 127.80 (C-2'), 133.96
20 (C-3'), 152.87 (C-2 C=O), 169.92 (C-4 C=O).

Schematic for Example 5

Schematic for Example 5



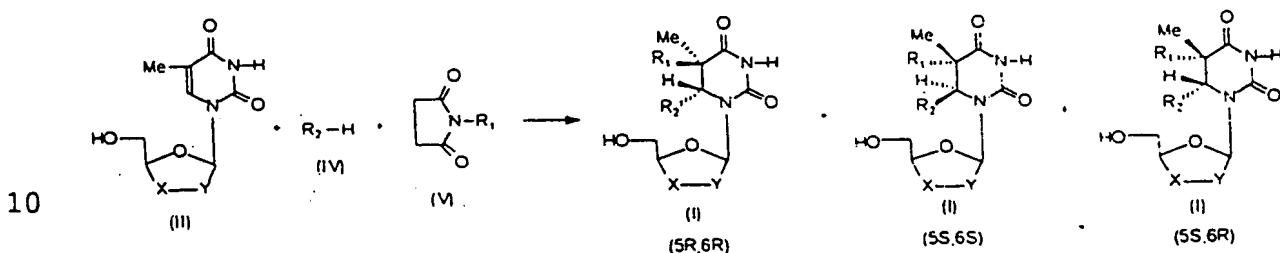
Example 6

30 Illustrates the preparation of 5-halo-6-alkoxy-
5,6-dihydrothymidines following the alternate method of
preparation seen in example 5 and described in the
35 schematic for Example 6.

-17-

Schematic for Example 6

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Schematic for Example 6

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Starting from the appropriately substituted compounds of formula (II), of formula (IV) and of formula (V), the following compounds of the formula (I) are prepared:

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TABLE (II)
5-halo-6-alkoxy-5,6-dihydrothymidine diastereomers prepared according to Example 6

| Chemical Name | No. | R ₁ | R ₂ | X-Y | R _f ^a | [α] _D ²⁵ (c, MeOH) | m.p. °C |
|---|------|----------------|----------------|-------------------------------------|-----------------------------|--|---------|
| (5R, 6R)-5-iodo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine | K-21 | 1 | O <i>Me</i> | CH(N ₃)—CH ₂ | 0.57 | +87.3° (0.0055) | oil |
| (5S, 6S)-5-iodo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine | K-22 | 1 | O <i>Me</i> | CH(N ₃)—CH ₂ | 0.63 | -46.2° (0.0037) | oil |
| (5R, 6R)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-23 | C1 | O <i>Me</i> | CH(F)—CH ₂ | 0.61 | +56.6° (0.0017) | oil |
| (5S, 6S)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-24 | C1 | O <i>Me</i> | CH(F)—CH ₂ | ND ^b | ND | oil |
| (5S, 6R)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-25 | C1 | O <i>Me</i> | CH(F)—CH ₂ | 0.55 | +32.2° (0.0016) | oil |
| (5R, 6R)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-26 | 1 | O <i>Me</i> | CH(F)—CH ₂ | 0.58 | +74.1° (0.0014) | oil |
| (5S, 6S)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-27 | 1 | O <i>Me</i> | CH(F)—CH ₂ | 0.66 | -83.0° (0.0035) | oil |
| (5R, 6R)-5-chloro-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine K-28 | C1 | O <i>Me</i> | CH=CH | 0.52 | c | +75.5° (0.0041) | 138-139 |
| (5S, 6S)-5-chloro-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine K-29 | C1 | O <i>Me</i> | CH=CH | 0.52 | c | ND | oil |
| (5R, 6R)-5-iodo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine K-30 | 1 | O <i>Me</i> | CH=CH | 0.54 | c | ND | oil |
| (5S, 6S)-5-iodo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine K-31 | 1 | O <i>Me</i> | CH=CH | 0.54 | c | ND | oil |

^aCHCl₃MeOH(9:1, v/v) Whatman 25 CM silica gel thin layer plates

^bND-not determined

^cSeparated by HPLC using a Whatman Partisil M9 10/25 ODS, C-18 reverse phase column using water-methanol as eluant at a flow rate of 2mL/min

Example 7

5 Preparation of 5-bromo-6-azido-5,6-dihydro-3'--azido-3'-deoxythymidine.

N-Bromosuccinimide (36 mg, 2 mmol) was added in aliquots to a precooled (-5°C) suspension prepared by mixing a solution of 3'-azido-3'-deoxythymidine (52 mg, 2 mmol) in dimethoxyethane (10 mL) and a solution of sodium azide (52 mg, 8 mmol) in water (0.125 mL) with stirring. 10 The initial yellow color produced upon addition of each aliquot of N-bromosuccinimide quickly disappeared. When all the N-bromosuccinimide had reacted, the reaction mixture was stirred for 30 min at 0°C, poured onto ice-water (25 mL) and extracted with ethyl acetate (3 X 50 mL). 15 Washing the ethyl acetate extract with cold water (10 mL), drying the ethyl acetate solution (Na_2SO_4) and removal of the solvent in vacuo gave a residue which was separated by silica gel column chromatography using chloroform as eluent to give a mixture of diastereomers (5R,6R)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine (K-34), 20 (5S,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine (K-35), and (5R,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine (K-36), respectively. 25 Analysis found: C, 30.69; H, 3.95; N, 28.77. $\text{C}_{10}\text{H}_{13}\text{BrN}_8\text{O}_4$ requires: C, 30.86; H, 3.36; N, 28.79.

Diastereomers K-34 and K-35: R_f 0.63; yield (30 mg, 38.6%); ^1H NMR (CDCl_3) δ 1.98 and 2.0 (two s, 3H total, CH_3), 2.30-2.74 (m, 2H total, H-2'), 2.94 (br s, 1H, 5'-OH, exchanges with deuterium oxide), 3.82-4.02 (m, 3H total, H-4' and H-5'), 4.30 and 4.36 (two m, 1H total, H-3'), 5.42 and 5.64 (two s, 1H total, H-6), 5.76 and 6.20 (two d, $J_{1',2'}=6.0$ Hz, 1H total, H-1'), 8.60 and 8.68 (two s, 1H total, NH, exchanges with deuterium oxide); ^{13}C NMR (CDCl_3) δ 22.76 and 23.08 (CH_3), 35.99 and

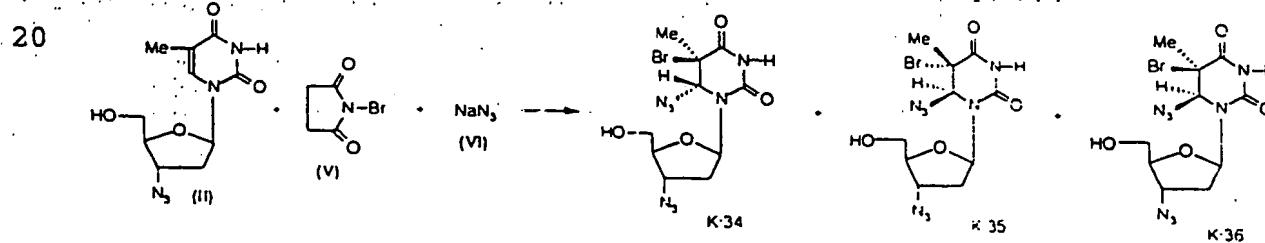
-20-

36.71 (C-2'), 52.31 and 52.79 (C-5), 60.04 and 60.52 (C-6),
 61.72 and 62.35 (C-5'), 73.88 and 76.64 (C-3'), 83.78 and
 5 84.22 (C-4'), 87.81 (C-1'), 149.88 and 150.02 (C-2 C=O),
 166.11 (C-4 C=O).

Diastereomer K-36: $[\alpha]_D^{25} = -47.5^\circ$ (c. 0.0016, MeOH); R_f 0.61; yield (20 mg, 25.7%); 1H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 2.24 and 2.34 (two m, 1H each, H-2'), 3.82-4.05 (m, 3H, H-4', H-5'), 4.37 (m, 1H, H-3'), 5.74 (s, 1H, H-6), 6.04 (d, $J_{1',2'}=6.0$ Hz, 1H, H-1'), 8.25 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 27.63 (CH_3), 36.02 (C-2'), 60.98 (C-6), 61.75 (C-5), 62.65 (C-5'), 74.75 (C-3'), 83.56 (C-4'), 85.05 (C-1'), 149.66 (C-2 C=O), 166.26 (C-4 C=O).

Schematic for Example 7.

Schematic for Example 7



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Example 8

Illustrates the preparation of 5-halo-6-azido-5,6-dihydrothymidines using a procedure similar to the one
 30 outlined in Example 7. Starting from the appropriately substituted compounds of formula (II), formula (V) and formula (VI), the following compounds are prepared:

- 21 -

TABLE (III)
5-halo-6-azido-5,6-dihydro-3'-deoxythymidine diastereomers prepared according to Example 8

| Chemical Name | No | R ₁ | R ₂ | X-Y | R _f ^a | [α] _D ²⁵ (c, MeOH) | Mp. °C |
|---|------|----------------|----------------|-------------------------------------|-----------------------------|--|--------|
| (5R, 6R)-5-chloro-6-azido-5,6-dihydro-5,6-dihydro-3'-azido-3'-deoxythymidine | K-37 | Cl | N ₃ | CH(N ₃)-CH ₂ | 0.63 ^b | ND ^c | oil |
| (5S, 6S)-5-chloro-6-azido-5,6-dihydro-5,6-dihydro-3'-azido-3'-deoxythymidine | K-38 | Cl | N ₃ | CH(N ₃)-CH ₂ | 0.63 ^b | ND | oil |
| (5S, 6R)-5-chloro-6-azido-5,6-dihydro-5,6-dihydro-3'-azido-3'-deoxythymidine | K-39 | Cl | N ₃ | CH(N ₃)-CH ₂ | 0.63 ^b | ND | oil |
| (5R, 6S)-5-chloro-6-azido-5,6-dihydro-5,6-dihydro-3'-azido-3'-deoxythymidine | K-40 | Cl | N ₃ | CH(N ₃)-CH ₂ | 0.63 ^b | ND | oil |
| (5R, 6R)-5-bromo-6-azido-5,6-dihydro-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-41 | Br | N ₃ | CH(F)-CH ₂ | 0.57 ^b | ND | oil |
| (5S, 6S)-5-bromo-6-azido-5,6-dihydro-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-42 | Br | N ₃ | CH(F)-CH ₂ | 0.57 ^b | ND | oil |
| (5S, 6R)-5-bromo-6-azido-5,6-dihydro-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-43 | Br | N ₃ | CH(F)-CH ₂ | 0.57 ^b | ND | oil |
| (5R, 6S)-5-bromo-6-azido-5,6-dihydro-5,6-dihydro-3'-fluoro-3'-deoxythymidine | K-44 | Br | N ₃ | CH=CH | 0.57 ^b | ND | oil |
| (5R, 6R)-5-bromo-6-azido-5,6-dihydro-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine | K-45 | Br | N ₃ | CH=CH | 0.57 ^b | ND | oil |
| (5S, 6S)-5-bromo-6-azido-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine | | | | | | | |

^aCHCl₃/MeOH (9:1, v/v) Whatman 25 OM silica gel thin layer plates^bNot separated by preparative HPLC^cND=not determined

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The compounds listed in the Examples, Tables I, II, and III have been found to have anti-human 5 immunodeficiency virus properties.

1. Anti-human immunodeficiency activity.

The test is designed to measure the efficacy against HIV for drugs acting at any stage of the virus reproductive cycle and involves the killing of T4 10 lymphocytes by HIV.

In order to test the activity of the compounds according to the invention, all tests were compared with at least one positive (e.g. AZT-treated) control done at the same time under identical conditions.

15 The test drug is dissolved in dimethylsulfoxide, then diluted 1:100 in cell culture medium before preparing serial half-log₁₀ dilutions. T4 lymphocytes (CEM cell line) are added and after a brief interval HIV-1 is added, resulting in a 1:200 final dilution of the test drug.

20 Uninfected cells with the test drug serve as a toxicity control, and infected and uninfected cells without the test drug serve as basic controls. Cultures are incubated at 37°C in a 5% CO₂ atmosphere for 6 days. The tetrazolium salt, XTT, is added to all wells, and cultures are incubated to allow formazan color development by viable cells.

25 Individual wells are analyzed spectrophotometrically to quantitate formazan production, and in addition are viewed microscopically for detection of viable cells and confirmation of protective activity. Test drug-treated virus-

30 infected cells are compared with test drug-treated non-infected cells and with other appropriate controls (untreated infected and untreated noninfected cells, test drug-containing wells without cells, etc.) on the same plate [see O.W. Weislow, R. Kiser, D. Fine, J. Bader, R.H.

35 Shoemaker, M.R. Boyd, J. Natl. Cancer Inst., 81, 577 (1989)]. The test results are shown in the following Table IV, the compounds listed being comparable to 3'-azido-3'-

TABLE (IV)

Anti-HIV activity of 5-halo-6-alkoxy (or azido)-5,6-dihydrothymidine diastereomers tested

| Substance | IC ₅₀ (M) ^a | EC ₅₀ (M) ^b | TI(₅₀ (IC ₅₀ /EC ₅₀) ^c |
|----------------------------------|-----------------------------------|-----------------------------------|--|
| K-1 | 1.72 x 10 ⁻⁵ | 3.27 x 10 ⁻⁹ | 5260 |
| K-2 | 4.25 x 10 ⁻⁵ | 2.80 x 10 ⁻⁷ | 152 |
| K-3 | 1.85 x 10 ⁻⁵ | 6.75 x 10 ⁻⁹ | 2740 |
| K-4 | 2.22 x 10 ⁻⁵ | 2.37 x 10 ⁻⁸ | 936 |
| K-10 | 1.72 x 10 ⁻⁶ | 5.25 x 10 ⁻⁹ | 328 |
| K-11 | 9.72 x 10 ⁻⁶ | 3.25 x 10 ⁻⁹ | 2991 |
| K-12/K-13 ^d | >1.28 x 10 ⁻⁴ | 5.46 x 10 ⁻⁵ | 2 |
| K-14/K-15 ^d | >1.40 x 10 ⁻⁵ | ND ^e | ND |
| K-19/K-20 ^d | >8.98 x 10 ⁻⁴ | 5.79 x 10 ⁻⁶ | 155 |
| K-21 | 1.87 x 10 ⁻⁵ | 3.17 x 10 ⁻⁹ | 5899 |
| K-22 | 6.42 x 10 ⁻⁶ | 5.15 x 10 ⁻⁹ | 1247 |
| K-23 | >8.0 x 10 ⁻⁵ | 5.55 x 10 ⁻⁸ | 144 |
| K-25 | >8.0 x 10 ⁻⁴ | 3.79 x 10 ⁻⁵ | 21 |
| K-26 | 5.73 x 10 ⁻⁵ | ND | ND |
| K-27 | 1.22 x 10 ⁻⁵ | 3.75 x 10 ⁻⁹ | 3253 |
| K-28/K-29 ^d | >1.03 x 10 ⁻³ | 3.75 x 10 ⁻⁴ | 2 |
| K-30/K-31 ^d | 6.60 x 10 ⁻⁵ | 3.75 x 10 ⁻⁷ | 178 |
| K-32 | >2.0 x 10 ⁻⁴ | ND | ND |
| K-33 | 2.0 x 10 ⁻⁴ | ND | ND |
| K-34/K-35 ^d | 1.76 x 10 ⁻⁴ | ND | ND |
| K-37/K-38/K-39/K-40 ^d | 3.5 x 10 ⁻⁴ | 1.49 x 10 ⁻⁶ | 235 |
| K-41/K-42/K-43 ^d | 1.0 x 10 ⁻⁴ | 1.45 x 10 ⁻⁸ | 6896 |
| K-44/K-45 ^d | 4.47 x 10 ⁻⁵ | 9.18 x 10 ⁻⁷ | 49 |
| AZT | 5 X 10 ⁻⁴ | 3 x 10 ⁻⁹ | |

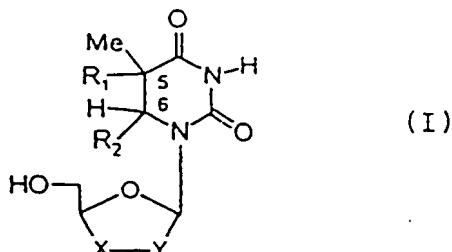
^aThe IC₅₀ value is the test drug concentration which results in a 50% survival of uninfected control cells (eg. cytotoxic activity of the test drug).^bThe EC₅₀ value is the test drug concentration which produces a 50% survival of HIV infected cells relative to uninfected controls (eg. in vitro anti-HIV activity)^cTherapeutic index^dTested as a mixture of diastereomers^eND = not determined

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We claim:

1. A dihydrothymidine derivative of the formula (I):

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or a non-toxic pharmaceutically acceptable salt thereof, wherein R₁ is a halogen substituent selected from the group consisting of iodo, bromo, chloro and fluoro; R₂ is a member selected from the group consisting of alkoxy wherein the alkyl moiety is a straight or branched chain having from 1 to 16 carbon atoms, hydroxy and azido; and X-Y is a member selected from the group consisting of CH(N₃)₂-CH₂, CH(F)-CH₂ and CH=CH.

15

2. A dihydrothymidine derivative according to Claim 1, wherein R₂ is a methoxy.

3. A dihydrothymidine derivative according to Claim 1, wherein R₂ is an ethoxy.

25

4. A dihydrothymidine derivative according to Claim 1, wherein R₂ is an isopropoxy.

30

5. A dihydrothymidine derivative according to Claim 1, wherein R₂ is a 1-octyloxy.

6. A dihydrothymidine derivative according to Claim 1, wherein R₂ is a 1-hexadecyloxy.

35

7. A dihydrothymidine derivative according to Claim 1, wherein R₂ is a hydroxy or an azido.

-25-

8. (5R, 6R)-5-bromo-6-methoxy-5, 6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 2.

5

9. (5S, 6S)-5-bromo-6-methoxy-5, 6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 2.

10. (5R, 6R)-5-bromo-6-methoxy-5, 6-dihydro-3'-fluoro-3'-
10 deoxythymidine according to Claim 2.

11. (5S, 6S)-5-bromo-6-methoxy-5, 6-dihydro-3'-fluoro-3'-
deoxythymidine according to Claim 2.

15 12. (5R, 6R)-5-bromo-6-methoxy-5, 6-dihydro-2', 3'-
didehydro-2', 3'-dideoxythymidine according to Claim 2.

13. (5S, 6S)-5-bromo-6-methoxy-5, 6-dihydro-2', 3'-
didehydro-2', 3'-dideoxythymidine according to Claim 2.

20

14. (5R, 6R)-5-chloro-6-methoxy-5, 6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 2.

25 15. (5S, 6R)-5-chloro-6-methoxy-5, 6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 2.

16. (5R, 6R)-5-iodo-6-methoxy-5, 6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 2.

30 17. (5S, 6S)-5-iodo-6-methoxy-5, 6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 2.

18. (5R, 6R)-5-chloro-6-methoxy-5, 6-dihydro-3'-fluoro-3'-
deoxythymidine according to Claim 2.

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19. (5S, 6S)-5-chloro-6-methoxy-5, 6-dihydro-3'-fluoro-3'-
deoxythymidine according to Claim 2.

20. (5S,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-
5 deoxythymidine according to Claim 2.
21. (5R,6R)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-
deoxythymidine according to Claim 2.
- 10 22. (5S,6S)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-
deoxythymidine according to Claim 2.
23. (5R,6R)-5-chloro-6-methoxy-5,6-dihydro-2',3'-
didehydro-2',3'-dideoxythymidine according to Claim 2.
- 15 24. (5S,6S)-5-chloro-6-methoxy-5,6-dihydro-2',3'-
didehydro-2',3'-dideoxythymidine according to Claim 2.
25. (5R,6R)-5-iodo-6-methoxy-5,6-dihydro-2',3'-
20 didehydro-2',3'-dideoxythymidine according to Claim 2.
26. (5S,6S)-5-iodo-6-methoxy-5,6-dihydro-2',3'-
didehydro-2',3'-dideoxythymidine according to claim 2.
- 25 27. (5R,6R)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 3.
28. (5S,6S)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 3.
- 30 29. (5R,6R)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-
didehydro-2',3'-dideoxythymidine according to Claim 3.
- 35 30. (5S,6S)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-
didehydro-2',3'-dideoxythymidine according to Claim 3.
31. (5R,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-

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deoxythymidine according to Claim 3.

5 32. (5S,6S)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 3.

33. (5S,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 3.

10 34. (5R,6R)-5-bromo-6-isopropoxy-5,6-dihydro-3'-azido-
3'-deoxythymidine according to Claim 4.

15 35. (5R,6R)-5-chloro-6-isopropoxy-5,6-dihydro-3'-azido-
3'-deoxythymidine according to Claim 4.

36. (5R,6R)-5-bromo-6-(1-octyloxy)-5,6-dihydro-3'-azido-
3'-deoxythymidine according to Claim 5.

20 37. (5R,6R)-5-chloro-6-(1-octyloxy)-5,6-dihydro-3'-
azido-3'-deoxythymidine according to Claim 5.

38. (5R,6R)-5-bromo-6-(1-hexadecyloxy)-5,6-dihydro-3'-
azido-3'-deoxythymidine according to Claim 6.

25 39. (5R,6R)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-
didehydro-2',3'-dideoxythymidine according to Claim 7.

40. (5S,6S)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-
30 didehydro-2',3'-dideoxythymidine according to Claim 7.

41. (5R,6R)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 7.

35 42. (5S,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-
deoxythymidine according to Claim 7.

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43. (5R,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

5

44. (5R,6R)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

10 45. (5S,6S)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

46. (5S,6R)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

15 47. (5R,6S)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

48. (5R,6R)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 7.

20

49. (5S,6S)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 7.

25 50. (5R,6S)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 7.

51. (5R,6R)-5-bromo-6-azido-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 7.

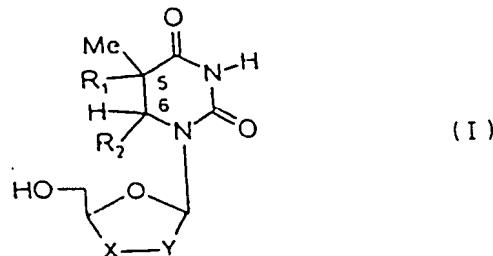
30 52. (5S,6S)-5-bromo-6-azido-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 7.

53. A method of preparing 5-halo-6-alkoxy-5,6-dihydro-

-29-

thymidine derivatives of formula (I) as in Claim 2 or 3 or 4 or 5 or 6:

5

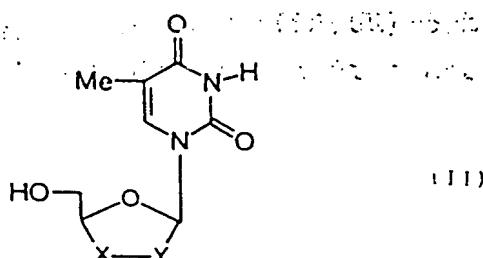


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wherein R₁ is a iodo, bromo, chloro or fluoro atom; R₂ represents a C₁-C₁₆ alkoxy group with a straight or branched alkyl chain and X-Z is CH=CH, CH(N₃)-CH₂ or CH(F)-CH₂ which comprises:

15 reacting a thymidine compound of formula (II):

20



25 with an electrophilic source of halogen of formula (III)

R₁-Z

wherein R₁ is as defined above and Z is independently a iodo, bromo or chloro atom.

30 In the presence of an alkyl alcohol of the formula (IV):

R₂-H

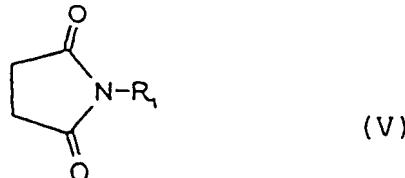
wherein R₂ is as defined above.

35 54. A method of preparing dihydrothymidine derivatives

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according to Claim 53, wherein the electrophilic source of halogen is:

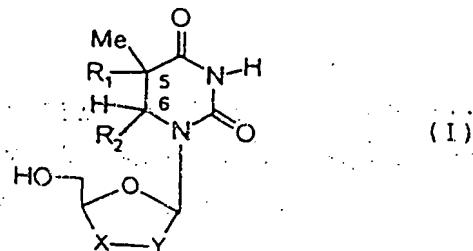
5



10 wherein R₁ is a iodo, bromo or chloro atom.

55. A method of preparing 5-halo-6-azido-5,6-dihydro-thymidine derivatives of formula (I) as in claim 7:

15

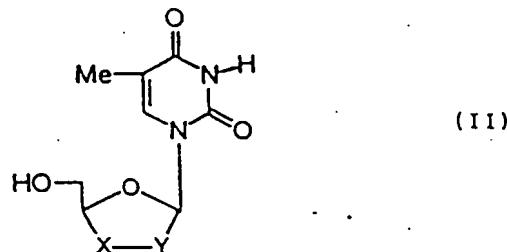


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wherein R₁ is a iodo, bromo, chloro or fluoro atom; R₂ is an azido group; and X-Z is CH=CH, CH(N₃) - CH₂ or CH(F)-C which comprises:

25

reacting a thymidine of formula (II)



30

with an electrophilic source of halogen of formula (III):



wherein Z is independently a iodo, bromo or chloro atom and
35 R₁ is as defined above.

In the presence of an alkali metal azide of the

-31-

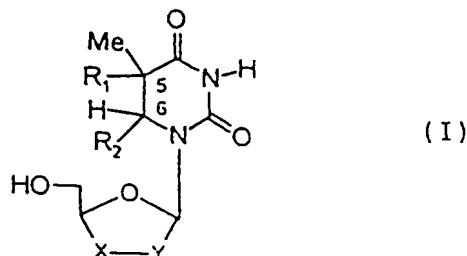
formula (VI):



5 wherein R_2 is as defined above and M is a sodium, selected from the group of sodium, lithium and potassium.

56. A method of preparing 5-halo-6-hydroxy-5,6-dihydro-thymidine derivatives of formula (I) as in claim 7:

10

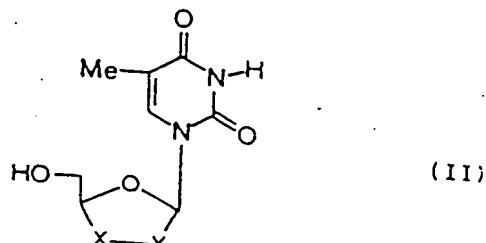


15

wherein R_1 is a iodo, bromo, chloro or fluoro atom; R_2 is a hydroxy radical; and $X-Z$ is $CH=CH$, $CH(N_3)-CH_2$ or $CH(F)-C$ which comprises:

reacting a thymidine of formula (II):

20



25

with an electrophilic source of halogen of formula (III):



wherein Z is independently a iodo, bromo or chloro atom and R_1 is as defined above.

30

In the presence of a solvent of formula (IV):



wherein R_2 is an hydroxy group.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07H 19/06, A61K 31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07H, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| P,X | Acta Cryst., Volume C49, 1993, H. Blanchard et al, "Structure of (+)-(5R,6R)-5-Chloro-6-methoxy-5, 6-dihydro-1-(2',3'-didehydro-2', 3'-dideoxy-beta-D-glycero-2-enopentofuranosyl)thymi- ne" page 246 - page 250 | 1-2,23-24, 53-54 |
| Y | SCIENCE, Volume 249, Sept 1990, H. Mitsuya et al, "Molecular Targets for AIDS Therapy" page 1533 - page 1544 -- | 1-56 |

 Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents
- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
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Date of the actual completion of the international search

Date of mailing of the international search report

17 March 1994

07 04 94

Name and mailing address of the International Searching Authority/Authorized officer



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EVA JOHANSSON

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| Y | STN International, File CA, Chemical Abstracts, volume 81, no. 25, 23 December 1974 (Columbus Ohio, US), B. Fouque et al: "Inhibition of Ehrlich ascites cell thymidine kinase by a new class of nucleoside derivatives", abstract no. 165382m, & Chemotherapy (Basel), 20(4), 221-6 1974 -- | 1-56 |
| A | STN International, File CA, Chemical Abstracts, volume 115, no. 11, 16 September 1991 (Columbus, Ohio, US), Lien Eric J. et al: "Physical factors contributing to the partition coefficient and retention time of 2'3'-dideoxynucleoside analogs", J. Pharm. Sci., 80(6), 517-21 -- | 1-56 |
| A | STN International, File CA, Chemical Abstracts, volume 114, no. 21, 27 May 1991 (Columbus, Ohio, US), Cretton Erika M. et al: "Catabolism of 3'-azido-3'-deoxythymidine in hepatocytes and liver microsomes, with evidence of formation of 3'-amino-3'-deoxythymidine, a highly toxic catabolite for human bone marrow cells", Mol. Pharmacol., 39(2), 258-66 -- | 1-56 |
| A | STN International, File CA, Chemical Abstracts, volume 110, no. 1, 2 January 1989 (Columbus, Ohio, US), Chu Chung K. et al: "Comparative activity of 2',3'-saturated and unsaturated pyrimidine and purine nucleosides against human immunodeficiency virus type 1 in peripheral blood mononuclear cells", Biochem. Pharmacol., 37(19), 3543-8 -- | 1-56 |
| A | STN International, File CA, Chemical Abstracts, volume 110, no. 13, 27 March 1989 (Columbus, Ohio, US), Chu Chung K. et al: "Structure-activity relationships of pyrimidine nucleosides as antiviral agents for human immunodeficiency virus type 1 in peripheral blood mononuclear cells", J. Med. Chem., 32(3), 612-17 ----- | 1-56 |